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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07C 321/28, 323/42, C07D 213/62, 213/70, 213/78, 277/06, 327/06, 339/02, 339/08, 401/12, 471/04, 487/04

A1

(11) International Publication Number: WO 98/42661

(43) International Publication Date: 1 October 1998 (01.10.98)

(21) International Application Number: PCT/IL98/00144

(22) International Filing Date: 26 March 1998 (26.03.98)

(30) Priority Data:
120531 26 March 1997 (26.03.97) IL

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: AROMATIC AND HETEROCYCLIC NITRATO DERIVATIVES

(57) Abstract

An organic compound is provided which contains at least one nitric oxide donor group and at least one group being, or being adapted to be converted in vivo to a free sulfhydryl group. A preferred compound contains at least one sulfhydryl group, either in the reduced –SH form or in the oxidized –S–S–disulfide form.

# AROMATIC AND HETEROCYCLIC NITRATO DERIVATIVES

## FIELD OF THE INVENTION

There are provided novel organic compounds and pharmaceutical compositions comprising same. The compounds are *in vivo* nitric oxide donors and they contain at least one sufhydryl group, either in the reduced -SH form or in the oxidized -S-S disulfide form.
Preferably the compounds containing the -S-S groups are five- or six membered heterocyclic compounds, where such a group is part of the heterocyclic nucleus, to which there may be attached directly or via a hydrocarbyl chain, which may be optionally substituted, one or more $-ONO_2$ groups.

The -S-S group may be a bridging member between to cyclic or two hereocyclic moieties each of which bears at least one $-ONO_2$ group.

Another suitable group of compounds comprises a 5- or 6-membered aromatic ring substituted with an -SH group and a $-ONO_2$ bearing group and there are also provided compounds having a 5-membered ring system containing a nitrogen and a non-adjacent S atom, substituted by at least one group bearing an $-ONO_2$ substituent and which may have also an -SH group as substituent.

All the above compounds are such that they will undergo *in vivo* metabolic cleavage to provide free -SH groups.

The novel compounds are effective substitutes for existing tolerance inducing organic or inorganic nitric oxide donors.

BACKGROUND OF THE INVENTION:

For over a century, the nitric oxide (NO) donor nitroglycerin (GTN) has been the mainstay in the treatment of angina and related heart diseases. However, the existing mechanisms proposing the mediation of GTN action by free NO, intracellular or extracellular S-nitrosothiol formation and subsequent activation of guanylyl cyclase (GC), as well as those describing GTN tolerance, have become increasingly controversial. The phenomenon of tolerance to GTN, however, is of special clinical importance. In fact, early tolerance to the anti-anginal effects of the drug is the major drawback of nitrate therapy, especially during acute myocardial infarction. This is particularly important since alternative non-tolerance inducing agents have not yet been developed to successfully replace therapy with GTN.

Based on accumulating evidence from our laboratory, we hypothesize that GTN may directly interact with SH-group/s located on its target enzyme (GC) resulting in its S-nitrosylation and activation. However, subsequent auto-oxidation (disulfide-formation) of these SH-groups render the enzyme inert towards further reaction with GTN, resulting in tolerance development.

Additionally, evidence has recently been provided to support an involvement of the superoxide anion in the mechanism/s

underlying GTN tolerance and cross-tolerance. According to these reports, increased production of superoxide anion was found to accompany tolerance development to GTN in vascular tissue. Treatment with superoxide dismutase (SOD), significantly enhanced relaxation of control and tolerant vascular tissue to GTN and other exogenous and endogenous vasodilators.

While the precise mechanism for the vasorelaxant effect of GTN is unknown, a consensus exists regarding the primary involvement of cGMP in mediating the nitrate-induced relaxation. However, the roles of sulfhydryl groups [reduced glutathione (GSH) and cysteine (Cys)] and of various enzymes in the bioconversion of GTN and subsequent activation of guanylyl cyclase (GC) leading to relaxation have become increasingly controversial. Cysteine was found to be the specific sulfhydryl required for activation of soluble coronary arterial GC and to be the only one of several sulfhydryls to react non-enzymatically with GTN at physiologic pH resulting in formation of S-nitrosocysteine [1,2]. Since S-nitrosothiols were shown to be potent activators of GC [3,4], S-nitroscysteine/thiol were proposed as the intracellular mediators of organic nitrate-induced vasorelaxation [5]. Additionally, N-acetylcysteine (NAC, an immediate donor of Cys thereby increasing GSH) was reported to potentiate GTN activity in vitro and in vivo [6-10]. The enhanced reaction of thiols with GTN in plasma and blood versus buffer suggested that activation of GC by GTN may be

mediated via extracellular formation of S-nitrosothiol/s [7]. In either case (intra or extracellular S-nitrosothiol formation), this association between sulfhydryls and GTN activity has long been recognized as evidence for the "thiol depletion hypothesis". However, recent studies from our laboratory [11] and those of Boesgard et al., [9] revealed a dissociation between tissue thiol content (measured as Cys and GSH) and nitrate tolerance in vivo.

In vitro inhibitory studies provide indirect support for the involvement of enzymes in GTN bioactivation [glutathione S-transferase (GST) and cytochrome P-450 (P-450)]. However, in view of several other reports suggesting the lack of any significant role of GST and P-450, in GTN bioactivation, the reduced bioactivation of GTN is unlikely to be the main factor underlying nitrate tolerance in vivo. In fact, reduced cGMP production was also shown to follow exposure of vascular preparation to direct NO-donors, for which no definitive metabolic pathway has been reported.

Furthermore, recent work from our laboratory presented in vivo evidence excluding the involvement of any particular metabolic pathway since reduced cGMP was also shown to follow treatment with S-alkylating agents in the absence of GTN

Each sulfhydryl may be present in a free form (SH), separately protected form (acetyl, carbamyl or other), or as an atom in a heterocyclic compound. In cases where the a compound contains two sulfhydryl groups, these can exist in the reduced (SH) or the oxidized (disulfide) form. However, each one of the compounds can also be regarded as a parent pro-drug which is assumed to undergo metabolic reduction or cleavage to provide the free SH groups in vivo.

Heart disease is the leading cause of death in Western society and is rapidly approaching this leading position worldwide. Ischemic heart disease (1HD) is the most common heart disease. For over a century, nitroglycerin and other organic nitrates have been used for the treatment of various types of myocardial ischemia, including acute myocardial infarction (AMI), and as adjuncts in the treatment of other heart diseases (congestive heart failure and resistant hypertension). Chronic prophylaxis and acute treatment are necessary to prevent complications of 1HD with potential fatal outcomes (~25% death for AMI). Tolerance to the anti-ischemic effect of these drugs is, by far, the most serious drawback of therapy with currently available organic nitrates. The compounds proposed in this application constitute a novel approach to overcome tolerance.

Because of their SH-content (radical scavenging and anti-oxidant properties), these compounds may also be applied for other pathologies.
Thus, considering their promising chemical and pharmacological characteristics and the ever increasing demand for better therapy for heart diseases significant potential exists for compounds of this type to become, the next generation of vasodilators. This is especially true concerning the considerable amount of recent evidence indicating the involvement of nitric oxide, reactive oxygen species and thiols in a variety of conditions, the pathogenesis of which as well as the treatment for, have not been fully resolved. These include (but not limited to): atherosclerosis, pulmonary and systemic hypertension, asthma and other related respiratory diseases, trauma, shock, neurotoxicity, neurodegenerative and

neurologic disorders, including those involving learning, memory, olfaction and nociception, Huntington, Alzheimer and Parkinson's diseases, multiple sclerosis and convulsive (seizure) disorders, AIDS-related disorders (i.e., dementia), disorders of gastric acid and other secretory and peristaltic functions of the alimentary system, drug and disease-induced neuropathy and nephropathy, pathological and premature uterine contractions, cellular defense impairment, and insulin-resistance in glucose intolerance and diabetes mellitus, pregnancy-induced hypertension, chemotaxis and phagocytic impairment in immunological disorders, cerebrovascular diseases, aggregation disorders, penile erection and treatment of male impotence [x-y].

Although the exact mechanisms defining organic nitrates and other nitric oxide-donors action and tolerance are not completely elucidated, the primary roles of nitric oxide (being their first messenger) and cGMP (the second messenger) in mediating vasorelaxtion is universally accepted. Our preliminary results utilizing example compounds 1 to 6 from Figure 1 show that, unlike currently available organic and inorganic nitrates, these compounds possess equipotent or even superior vasorelaxant activity. Moreover, using cGMP measurements both in vitro and in vivo show that these compounds do not produce tolerance even after extended periods of exposure to the drug when used, for example, in nitroglycerin-equimolar dosing regimens for which tolerance to the cGMP-inducing activity of nitroglycerin has been documented under the same experimental conditions (Table 1).

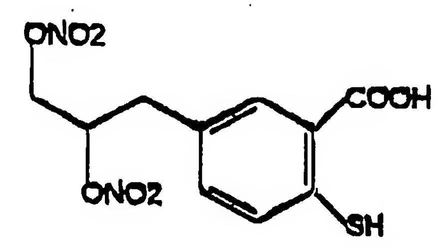
According to this invention, whenever a compound exists in the acid form, the term 'acid' should also be understood to include the corresponding acid halide, salts with pharmacologically acceptable alkali metal (including alkaline earth metal and ammonium bases), ester and amides. Moreover, the alcohol or the amines used to form the corresponding ester and amides of the acid can also bear a nitrate ester.

The present invention is concerned with pharmaceutical compositions, with new pharmaceutically-active compounds, the methods of their use and with the preparation thereof.

The invention relates to nitric oxide donors, being an organic compound containing at least one nitric oxide donor group, and at least one group being, or being adapted to be converted *in vivo* to a free sulfhydryl group. Preferred are compounds which contains at least one sulfhydryl group, either in the reduced - SH form or in the oxidized -S-S-disulfide form.

Preferred are such compounds which contain a 5- or 6-membered ring which, contains 2 conjugate -S- atoms, substituted by one or more $-ONO_2$ groups or linked to one or more substituents bearing a terminal $-ONO_2$ group, or where the -S-S-group is in an open configuration, linked to at least one aromatic nucleus or a heterocyclic nucleus with a nitrogen in the ring structure, which rings beȧr a substituent with a terminal -ONO2 group or where the compound is a five-membered hetrocycle containing a -S- atom and a nitrogen substituted with at least one substituent with a terminal $-ONO_2$ group.

Specific new compounds are:



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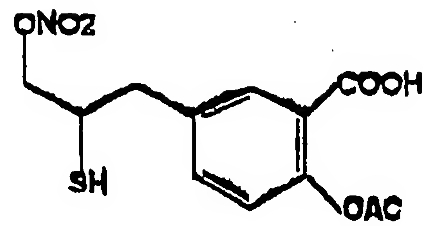

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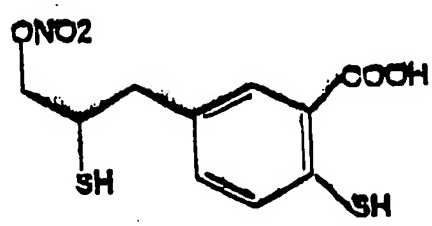

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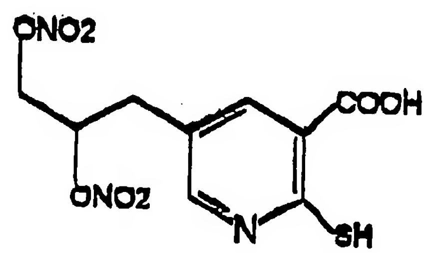

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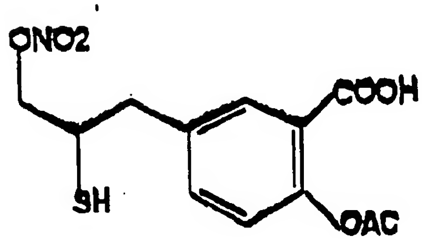

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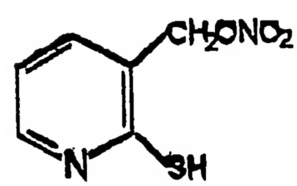

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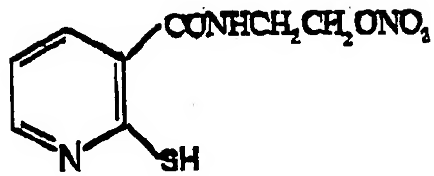

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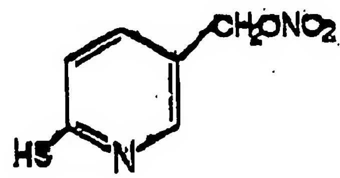

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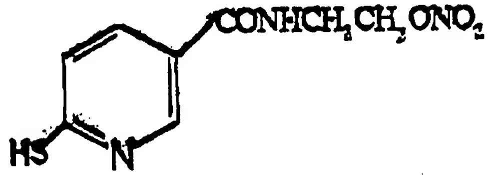

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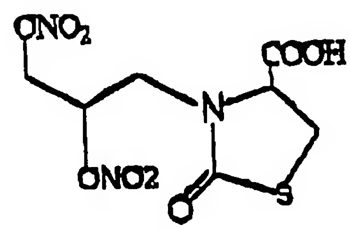

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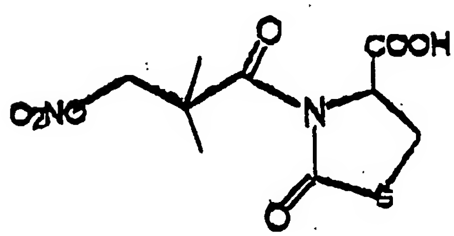

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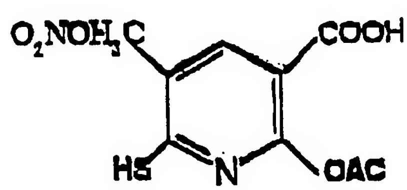

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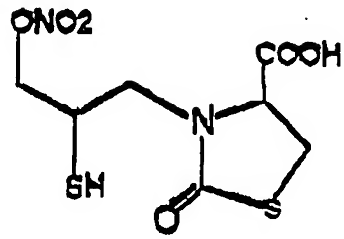

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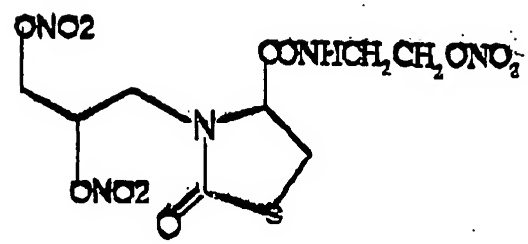

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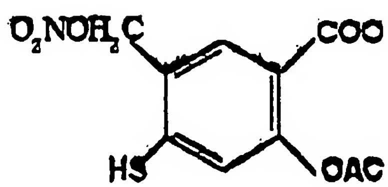

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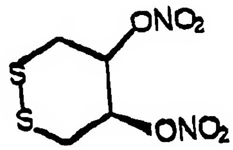
Another type of novel compound is



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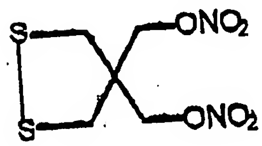

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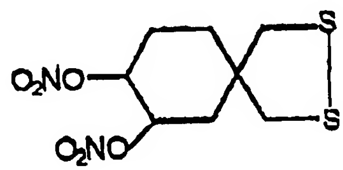

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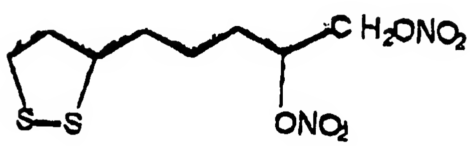

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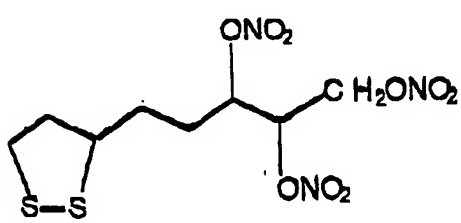

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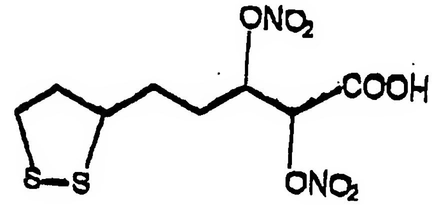


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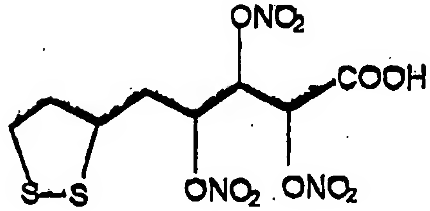


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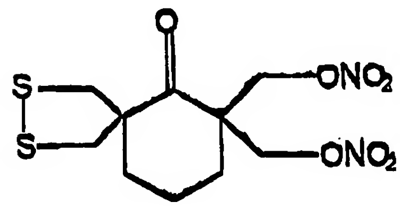


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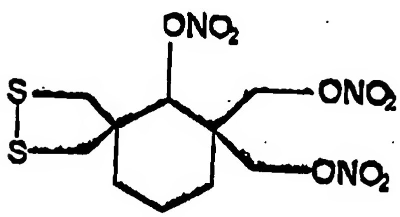


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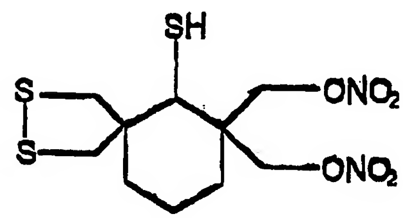


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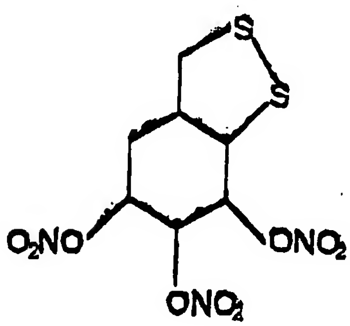


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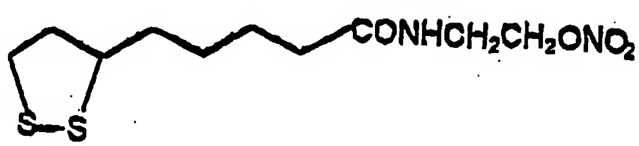


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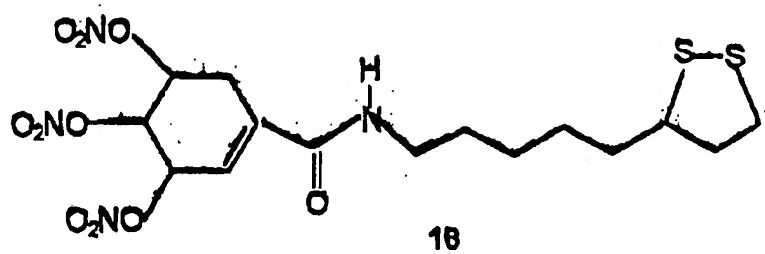

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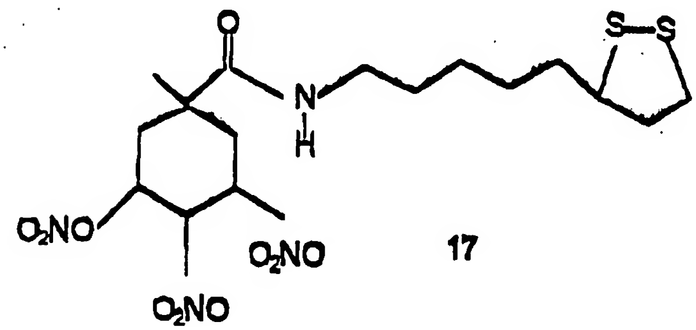

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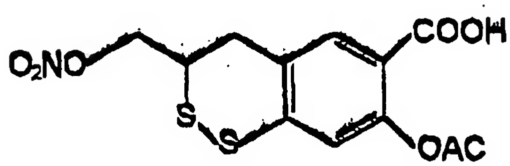

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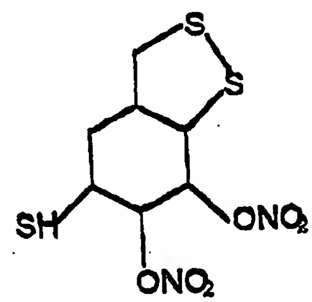

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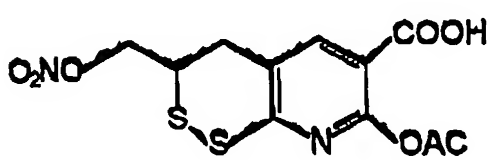

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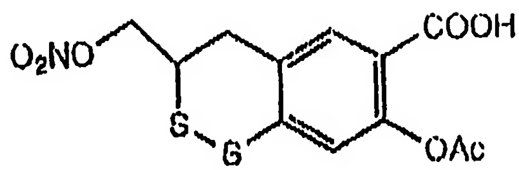


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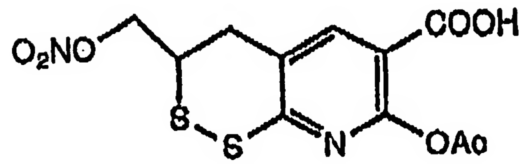


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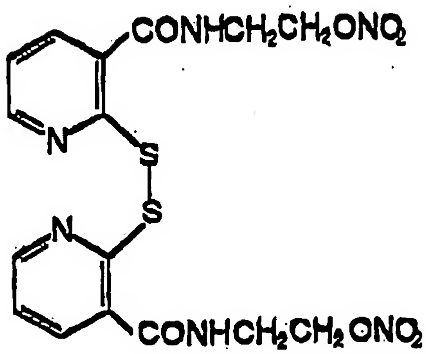


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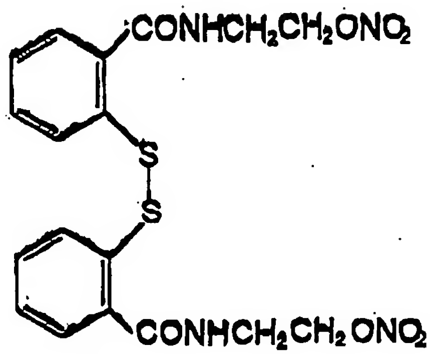


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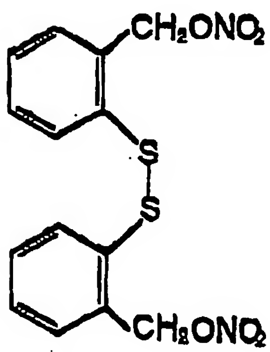


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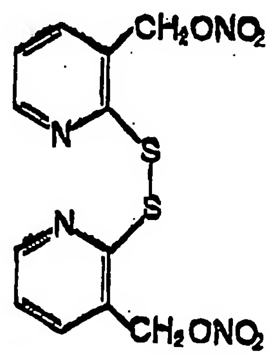


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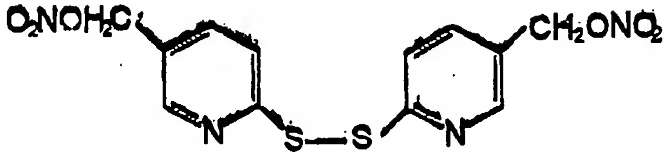

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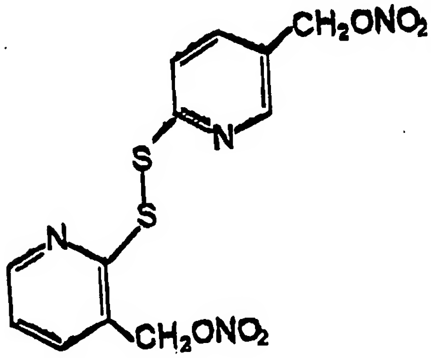

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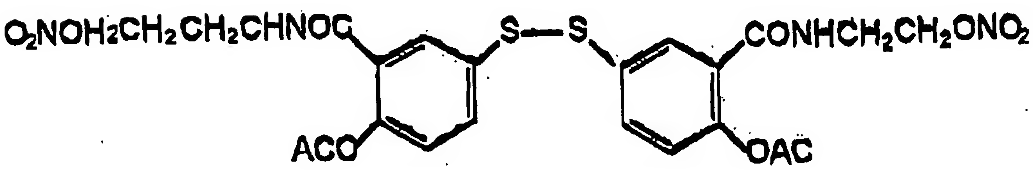

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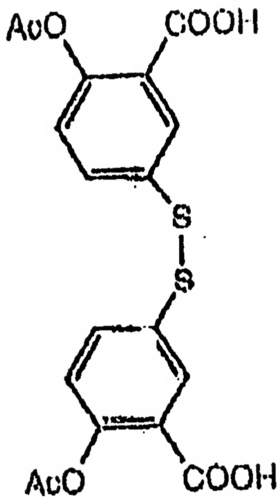
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COOH
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AcO
COOH

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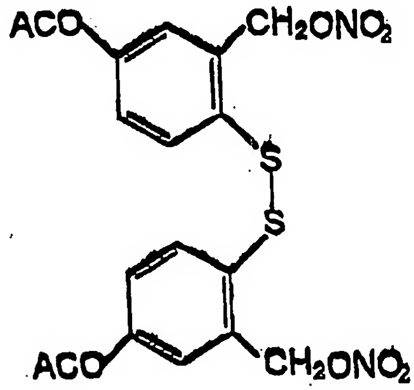
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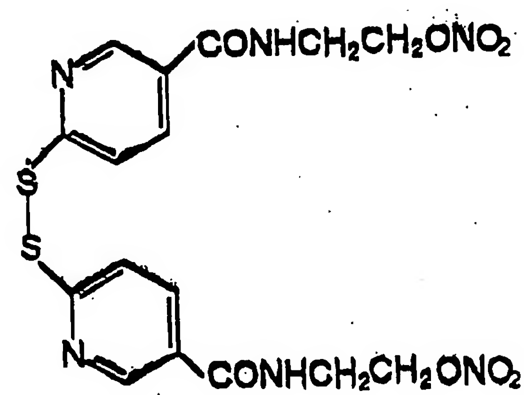
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S
S
N
CONHCH2CH2ONO2

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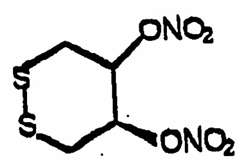
The invention also relates to pharmaceutical composition for the treatment of disorders where nitric oxide donors are indicated, which comprises as active ingredient an organic compound containing at least one nitric oxide donor group, and at least one group being, or being converted *in vivo* to a free sulfhydryl group, as defined above. Such a compound can be one which contains at least one sulfhydryl group, either in the reduced -SH form or in the oxidized -S-S disulfide form.

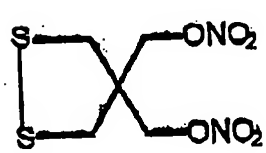
Preferred are compositions where the active compound contains a 5- or 6-membered ring compound containing 2 conjugate -S-.atoms, substituted by one or more -$ONO_2$ groups or linked to one or more substituents bearing a terminal -$ONO_2$ group, or where the -S-S group is in an open configuration, linked to at least one aromatic nucleus or a heterocyclic nucleus with a nitrogen in the ring structure, which rings bear a substituent with a terminal -$ONO_2$ group or where the compound is a five-membered hetrocycle containing a -S- atom and a nitrogen substituted with at least one substituent with a terminal -$ONO_2$ group.

Preferred compositions contain as active ingredient a compound such as:




1


2

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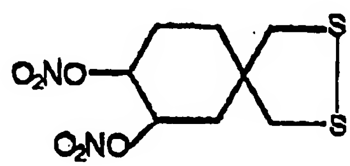


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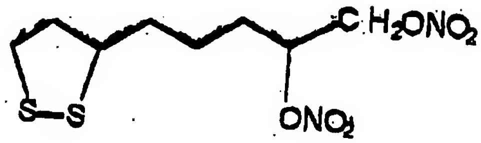

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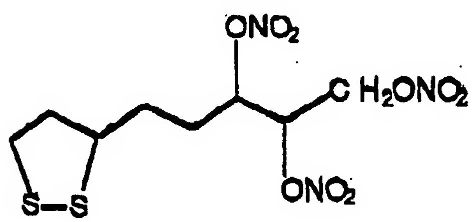

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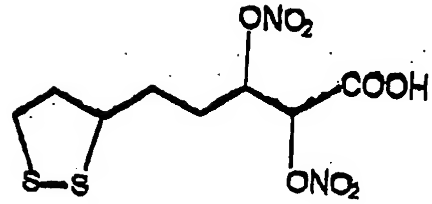

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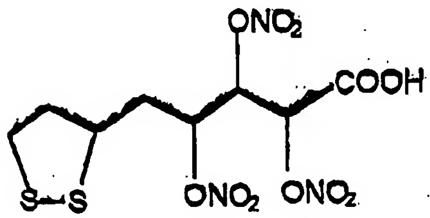

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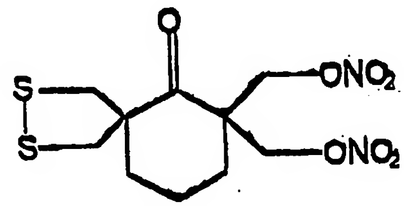

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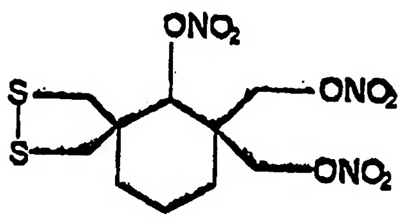

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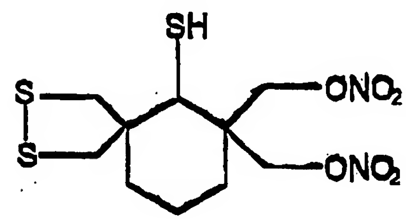

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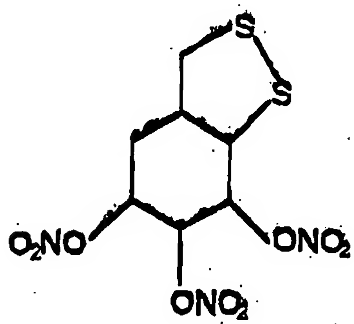

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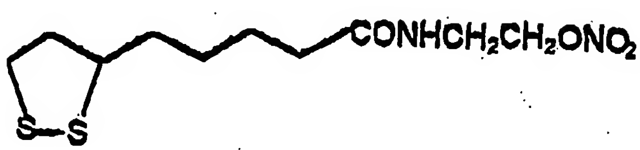

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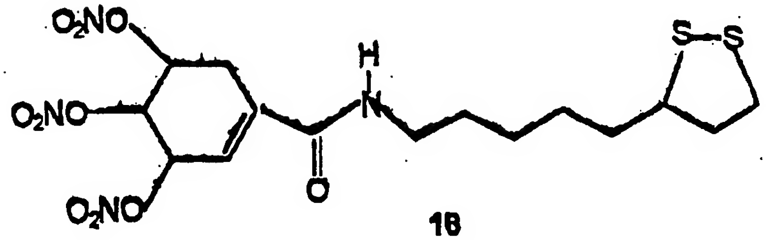
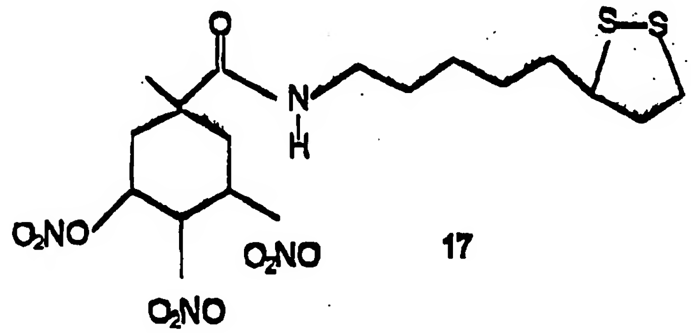
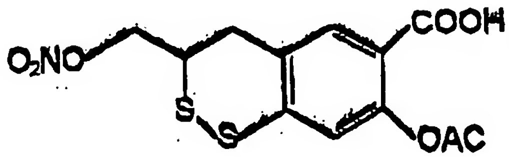

O2NO
O2NO
O2NO
H
N
O
S-S

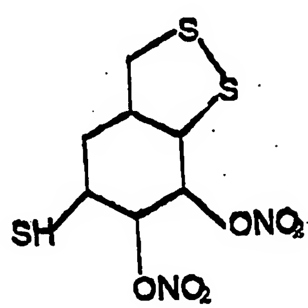
16


O
N
H
S-S
O2NO
O2NO
O2NO

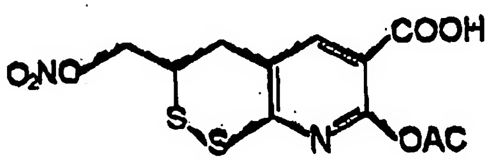
17


O2NO
COOH
S
S
OAC

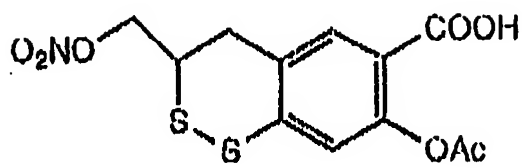
18


S
S
SH
ONO2
ONO2

19


O2NO
COOH
S
S
N
OAC

20



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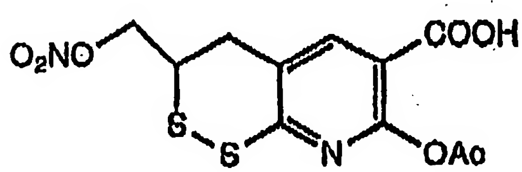

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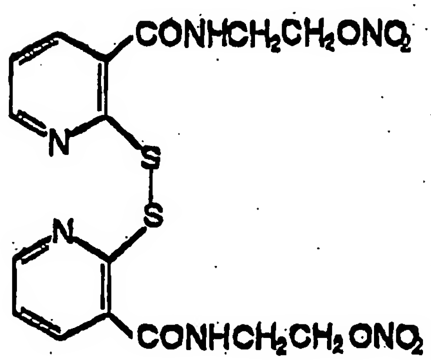

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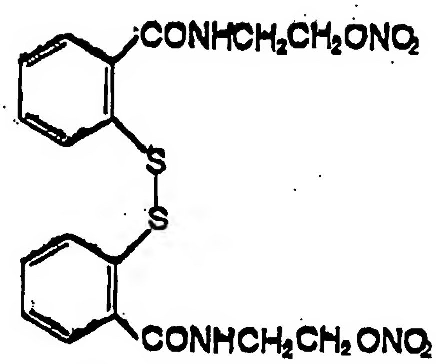

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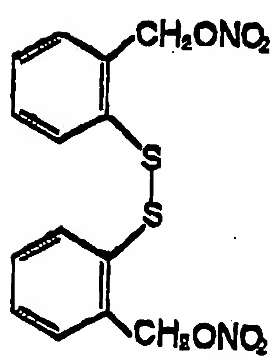

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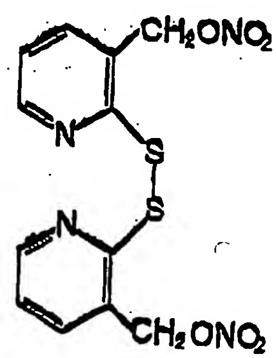

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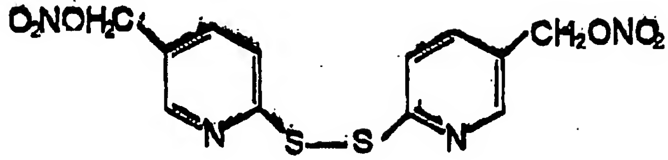

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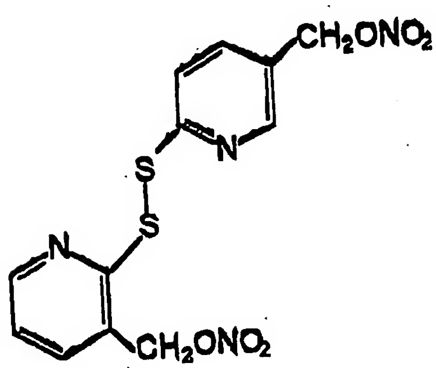

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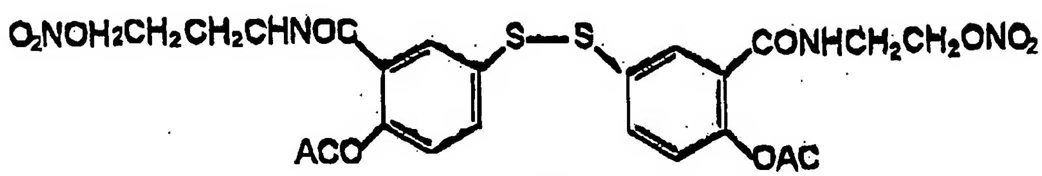

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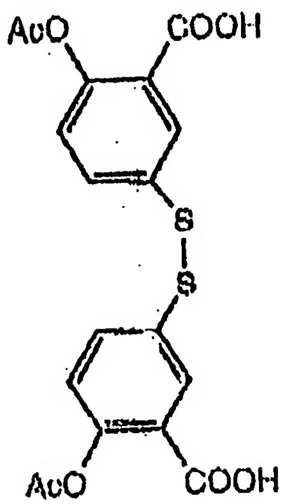
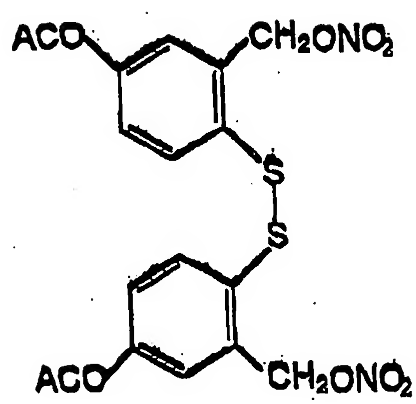
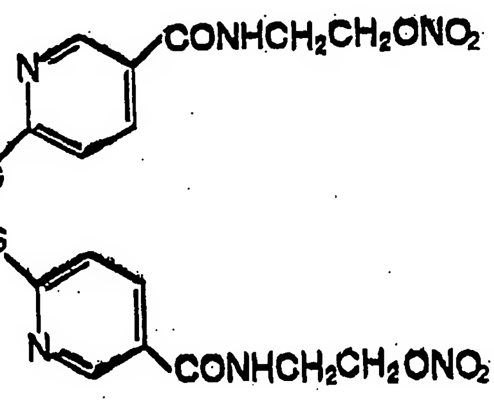

AcO
COOH
S
S
AcO
COOH

30

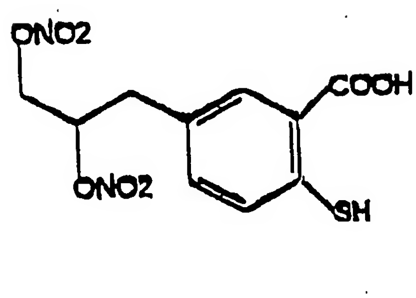

ACO
$CH_2ONO_2$
S
S
ACO
$CH_2ONO_2$

31


N
$CONHCH_2CH_2ONO_2$
S
S
N
$CONHCH_2CH_2ONO_2$

32

Other pharmaceutical compositions are those where the active compound is selected from:

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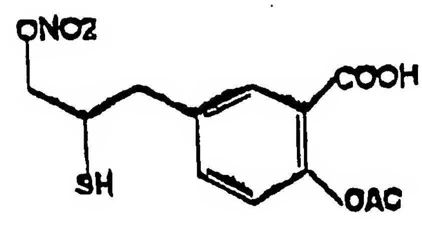


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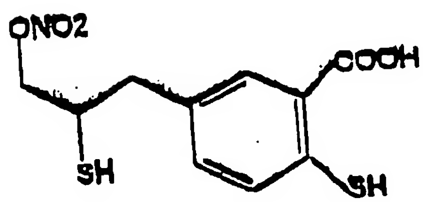


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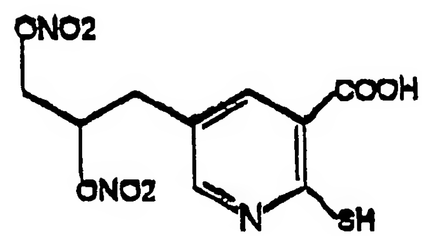


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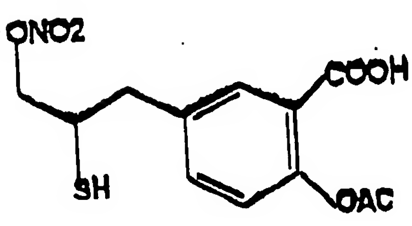


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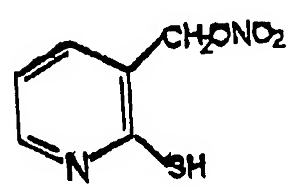


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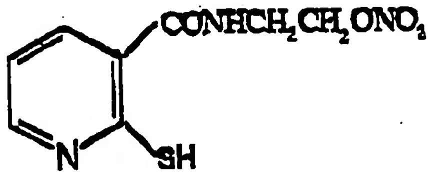

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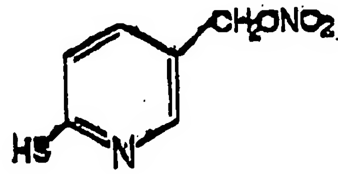

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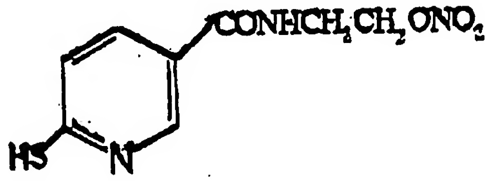

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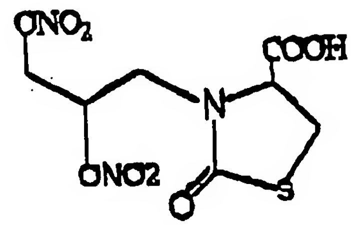

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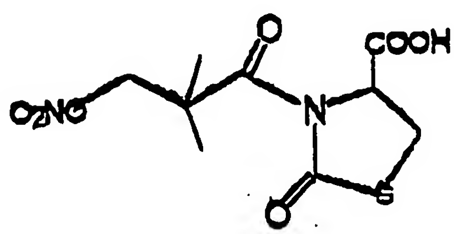

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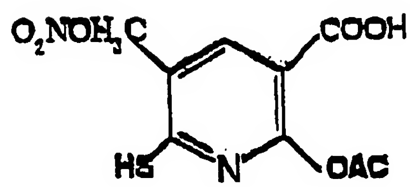

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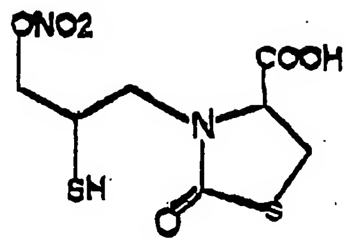
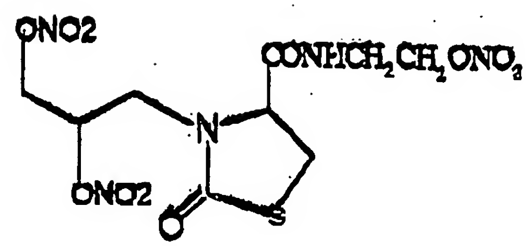
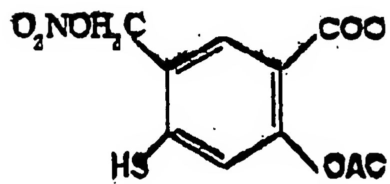

ONO2
COOH
N
SH
O
S

13


ONO2
CONHCH2CH2ONO2
N
ONO2
O
S

14


O2NOH2C
COO
HS
OAC

15

For the preparation of pharmaceutical compositions, the novel compounds are mixed in the usual way with appropriate pharmaceutical carrier substances, aroma, flavoring and coloring materials and formed, for example, into tablets or dragees of immediate or sustained release or, with additions of appropriate adjuvants, for example, water or an oil, such as olive or other oil, are suspended or dispersed or dissolved.

The compounds or the pharmaceutical composition thereof can be administered orally (including the sublingual and buccal routes) or via an injectable from (including the subcutaneous, intramuscular, intraperitoneal and the parenteral routes). Other routes of administration such as aerosols and dermal preparations are also to be considered. As injection medium, water is preferably used which contains the stabilizing agents, solubilizing agents and/or buffers usually utilized in the preparations of solutions for injections. Such additives include, for example, tartarate and borate buffers, ethanol, ethylene and propylene glycols, glycerol, dimethyl sulphoxide, complex formers (i.e., ethylenediamine tetraacetic acid), high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation and polyethylene derivatives of sorbit anhydrides. Solid carrier materials include, for example, starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acid, high molecular weight polymers (i.e., polyethylene glycol). Compositions suitable for oral administration (as defined above) can, if necessary, contain flavoring and sweetening agents.

It will be understood that the compounds shown demonstrate the principal upon which this invention is based. Thus, the specification and examples given in this application are illustrative but not limitative of the present invention and that embodiments within the spirit and scope of the invention will suggest themselves to those skilled in the art.

The synthesis of the novel compounds carried out utilizing conventional organic synthetic methods. The following examples are given for the purpose of illustrating the present invention:

Example 1:

*trans*-1,2-Dinitrato-4,5-dithiane (compound 1, Figure 1)

This compound was easily synthesized utilizing the commercially available precursor *trans*-1,2-dihydroxy-4,5-dithiane. 0.5g of the precursor was added portionwise to chilled (-5° C) 1:1 mixture of fuming nitric sulfuric acids. Upon completion of the addition, the ice/salt bath was removed and the mixture brought to room temperature. This mixture was added dropwise to a cooled mixture of dry diethyl ether:acetonitrile:water (70:20:10) with vigorous stirring. The lower aqueous phase was separated and extracted twice with diethyl ether. The combined organic extracts were washed twice with water and once with cold 1% sodium carbonate solution. The organic layer was dried over magnesium sulfate, and evaporated to near dryness under reduced pressure. The residual oil was loaded on a silica column and separated after elution with hexane. Evaporation under reduced pressure of the eluate yielded a yellowish oil (0.56g) with analytical data consistent with the structure of *trans*-1,2-dinitrato-4,5-dithiane.

Example 2:

2,2'-Dithiodiethanol-dinitrate (compound 2, Figure 1)

This compound was synthesized in a similar fashion as compound 1 above using the commercially available precursor 2,2'-dithiodiethanol as the starting material. The precursor was nitrated and separated as above yielding the title compound 2,2'-dithiodiethanol-dinitrate.

Example 3:

<u>1,1-Diemethanol-dinitrate-3,4-dithiane (compound 3, Figure 1)</u>

This compound was synthesized by bishydroxymethylation of diethyl malonate followed by thiolation of the hydroxyl groups (via the halide intermediate). The resulting 1,1-dicarboxy-3,4-dithian was reduced by borane (catechol borane solution) to the corresponding 1,1-diemethanol-3,4-dithiane. Direct nitration of this latter intermediate yielded the title compound 1,1-diemethanol-dinitrate-3,4-dithiane.

Example 4:

<u>1,1'-Bisthiomethyl-3,4-dihydroxy-cyclohexane-dinitrate ester</u>

This compound was synthesized by thiolation of the dichloride intermediate of the commercially available 1,1'-bishydroxymethyl-3-cyclohexene. Oxidation of the double bond either by hydrogen peroxide/osmium tetroxide to generate the *cis*-diol or by a peracid/formic acid mixture to generate the *trans*-diol followed by nitration of the diol will generate the corresponding *(cis* or *trans)* form of the title compound.

Example 5:

<u>Thioctyl alcohol nitrate ester (compound 5, Figure 1)</u>

This compound was synthesized in a high yield process utilizing thioctic acid as the precursor. Following reduction of the acid (or its methyl or ethyl ester) by catechol borane solution, the resulting thioctyl alcohol was separated and nitrated as described above to yield the title compound.

Example 6:

<u>1,2-Dihydroxy-dinitrate-6,8-dithiane (compound 6, Figure 1)</u>

2-Hydroxy lipoic (thioctic) acid was synthesized from thioctic acid via the 2-bromo derivative. This intermediate was reduced via borane to yield the direct precursor

1,2-dihydroxy-6,8-dithiane which, upon nitration as described above, yielded the title compound.

## Experimental Report

Representative for the new compounds, the vasorelaxant activities (measured as the ability of the tested drug to induce an increase in vascular cGMP) of the example compounds 1 to 6 were determined and compared to activity of nitroglycerin under the same experimental conditions following single and sustained exposure of rats to the compound.

For this purpose the compound to be tested was administered, in each case, to 8 male Sprague-Dawley rats (300-400g) before and after an 18 hr continuous intravenous infusion of the compound. The 18 hr continuous infusion period was determined based on existing data demonstrating the development of tolerance to the drug effect in the case of nitroglycerin. The existence of tolerance to the drug is demonstrated by the inability of the drug to attain 50% or more of the cGMP values measured in the vascular tissue after dosing of the drug to previously treated animals as compared to controls (non-treated or vehicle-treated animals). After drug administration (i.v. push), the rat was sacrificed, the aorta immediately removed and processed for cGMP measurement as has been described in detail by us (z). All of the tested new compounds were utilized in nitroglycerin-equimolar doses, either before or after the 'tolerance' induction period.

The following table summarizes the results obtained following administration of either nitroglycerin or the tested compounds before and after an 18 hr continuous exposure to the same compound:

| | cGMP (pmol/g tissue) | |
|---|---|---|
| Tested Compound | Pre-infusion | Post-infusion |
| Nitroglycerin | 153 ± 13 | 68 ± 9** |
| Compound 1 | 196 ± 14 | 189 ± 13* |
| Compound 2 | 169 ± 12 | 174 ± 13* |
| Compound 3 | 171 ± 14 | 174 ± 16* |
| Compound 4 | 149 ±11 | 169 ± 13* |
| Compound 5 | 123 ± 13 | 113 ± 11* |
| Compound 6 | 193 ± 17 | 179 ± 12* |

**Signficantly different from the pre-infusion values and denotes tolerance.

*Not significantly different from pre-infusion levels and denotes the lack of tolerance.

Besides their expected superior vasorelaxant activity, these results clearly demonstrate that whereas tolerance to the cGMP-inducing activity of nitroglycerin developed early (18 hr) following its continuous in vivo administration, no tolerance was observed to the cGMP-increasing effects of the novel compounds under the same experimental conditions used for the induction of in vivo tolerance. In fact, preliminary results from ongoing experiments in our laboratory show that no tolerance to this cGMP-inducing effect of these novel SH-containing-NO-donors develop even after exposure of the animals to the compounds for extended periods of time (i.e., not even after 168 hr of continuous intravenous infusions).

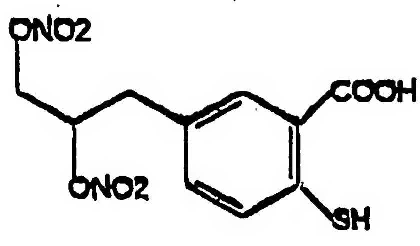
## CLAIMS

1. A nitric oxide donors being an organic compound containing at least one nitric oxide donor group, and at least one group being, or being adapted to be converted *in vivo* to a free sulfhydryl group.

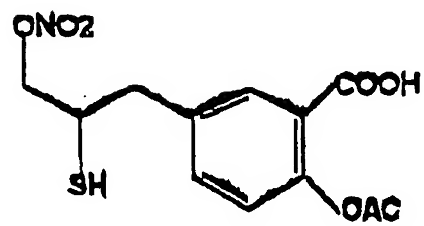
2. A compound according to claim 1, which contains at least one sulfhydryl group, either in the reduced -SH form or in the oxidized -S-S disulfide form.

3. A compound according to claim 1 or 2, which contains a 5- or 6-membered ring compound containing 2 conjugate -S- atoms, substituted by one or more $-ONO_2$ groups or linked to one or more substituents bearing a terminal $-ONO_2$ group, or where the -S-S group is in an open configuration, linked to at least one aromatic nucleus or a heterocyclic nucleus with a nitrogen in the ring structure, which rings bear a substituent with a terminal $-ONO_2$ group or where the compound is a five-membered hetrocycle containing a -S- atom and a nitrogen substituted with at least one substituent with a terminal $-ONO_2$ group.

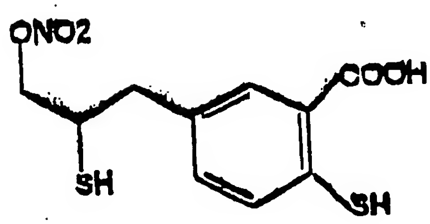
4. A compound according to claim 1 selected from:


ONO2
COOH
ONO2
SH

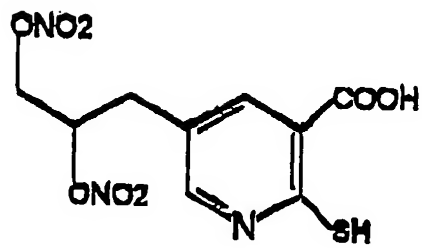
1


ONO2
COOH
SH
OAC

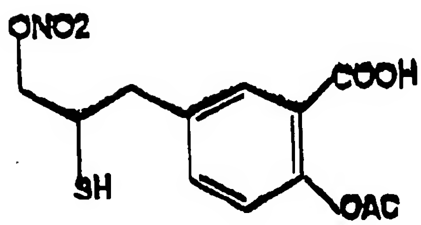
2


ONO2
COOH
SH
SH

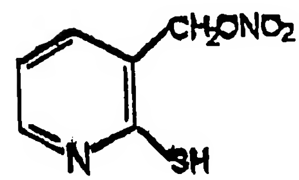
3


ONO2
COOH
ONO2
N
SH

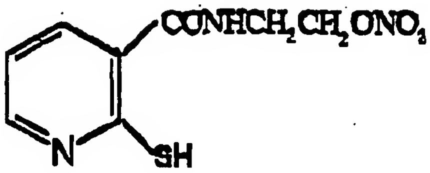
4


ONO2
COOH
SH
OAC

5


CH2ONO2
N
SH

6



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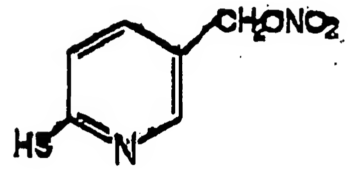

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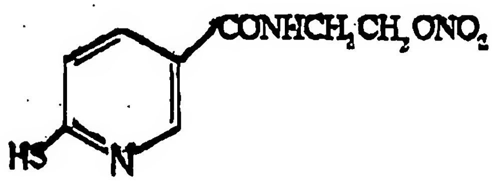

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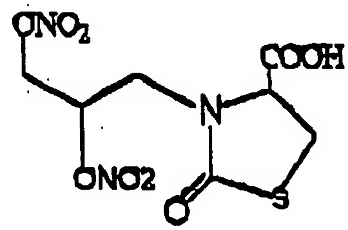

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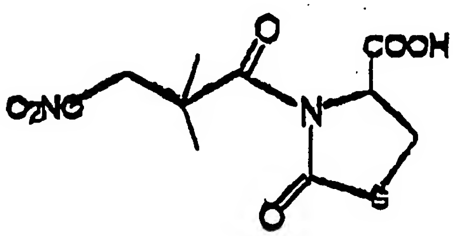

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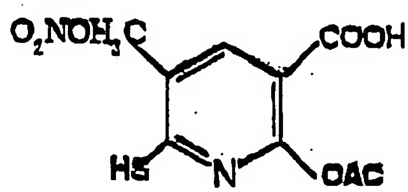

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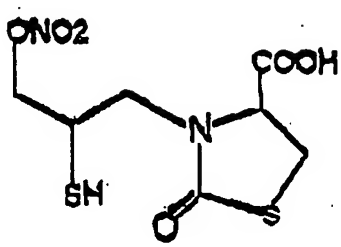
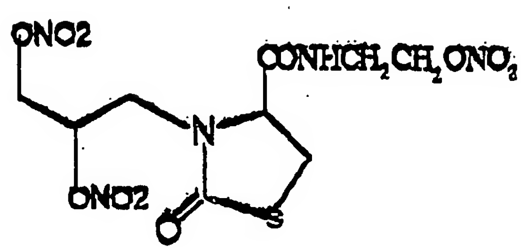
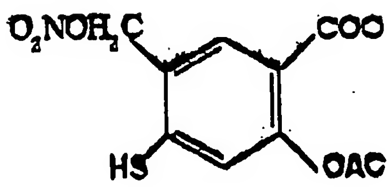

ONO2
COOH
N
SH
O
S

13

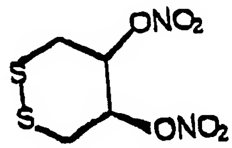

ONO2
CONHCH2CH2ONO2
N
ONO2
O
S

14


O2NOH2C
COO
HS
OAC

15

5. A compound according to claim 1, selected from



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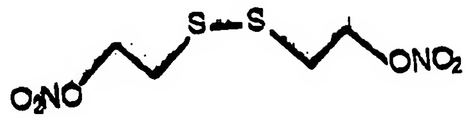

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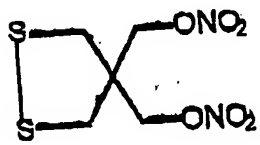

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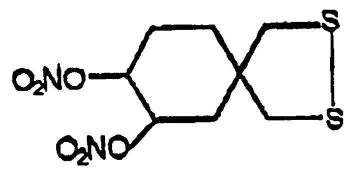

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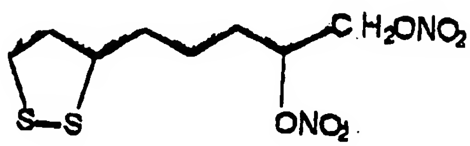

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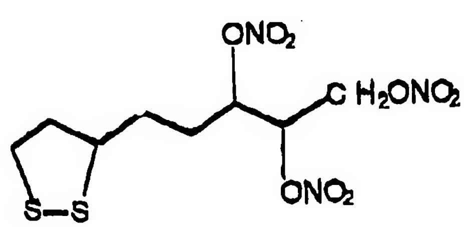

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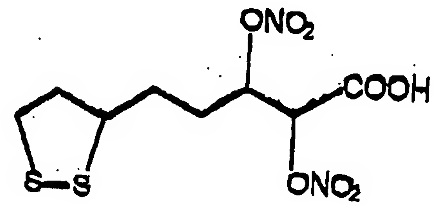

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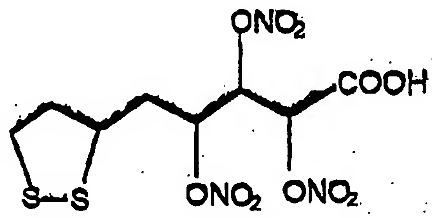

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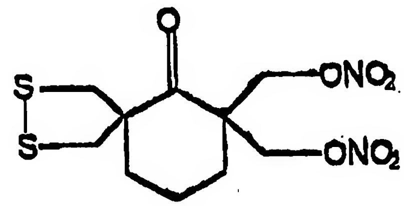

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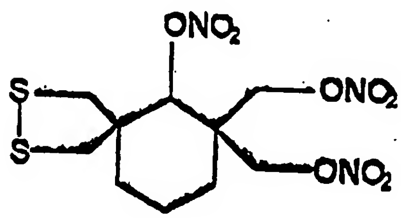

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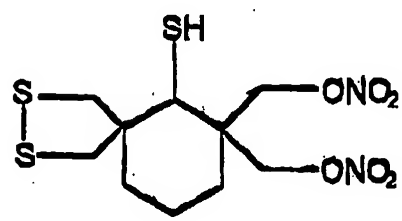

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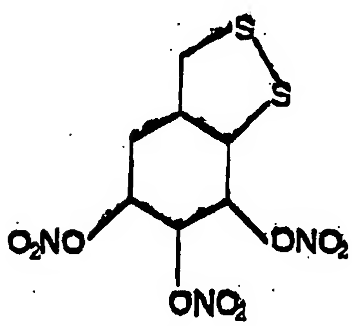

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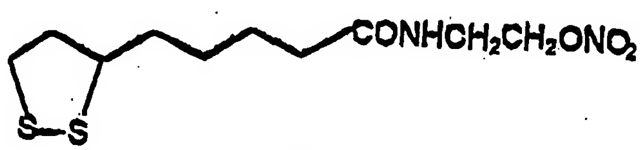

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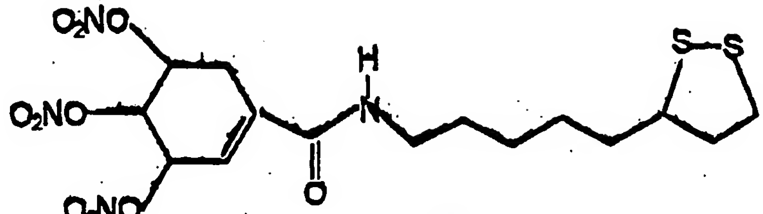
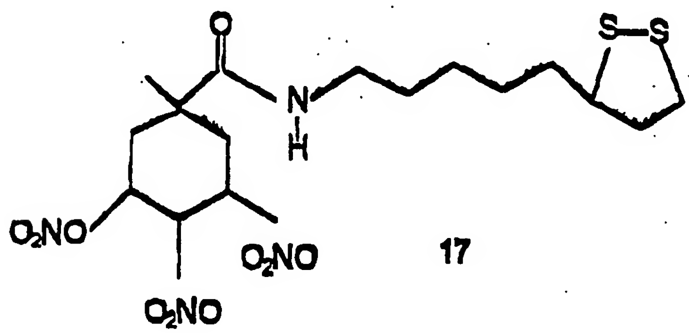
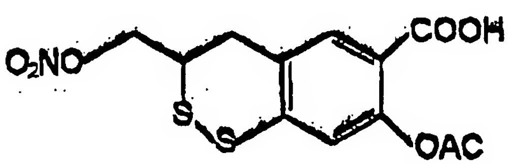

O2NO
O2NO
O2NO
H
N
O
S–S

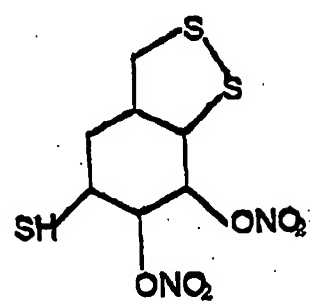
16


O
S–S
N
H
O2NO
O2NO
O2NO

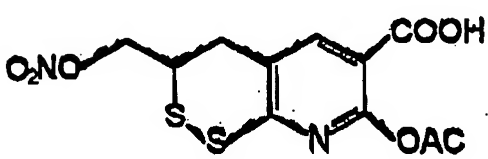
17


O2NO
COOH
S
S
OAC

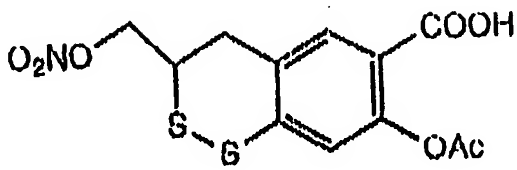
18


S
S
SH
ONO2
ONO2

19


O2NO
COOH
S
S
N
OAC

20



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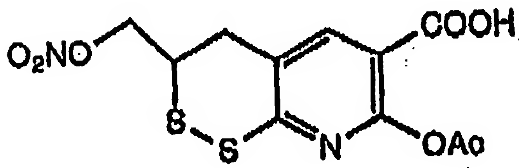

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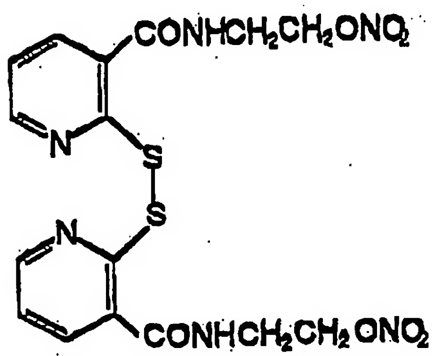

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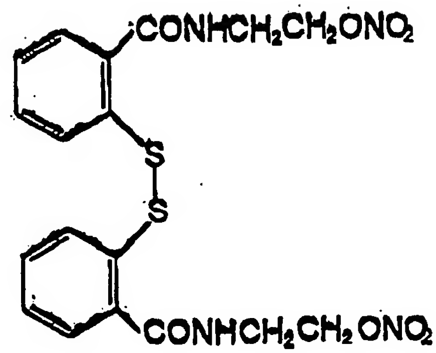

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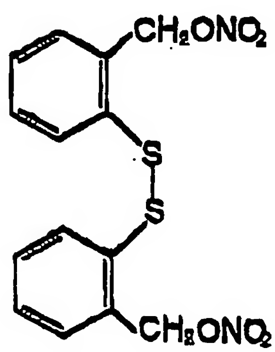

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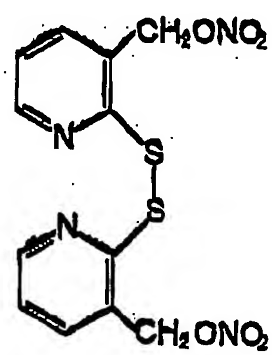

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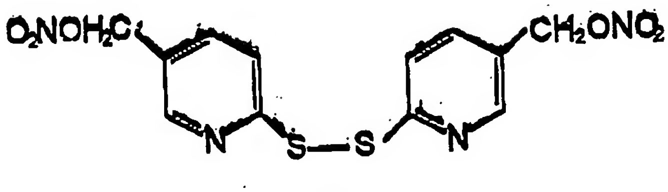

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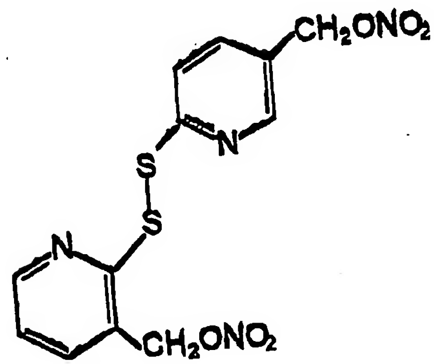

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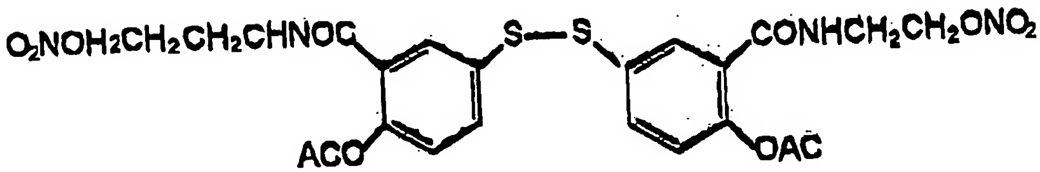

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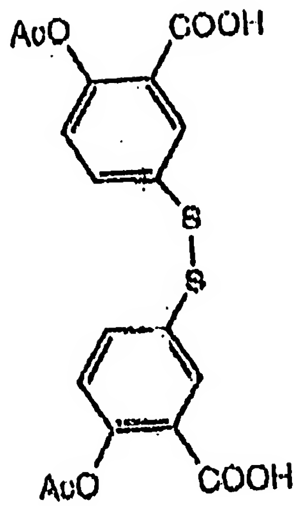
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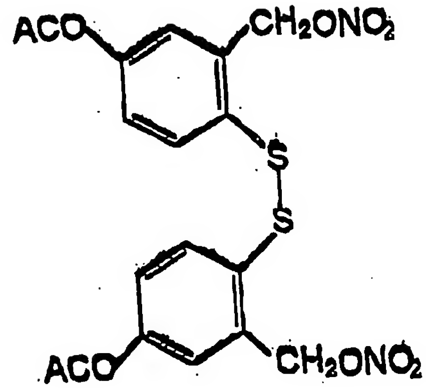
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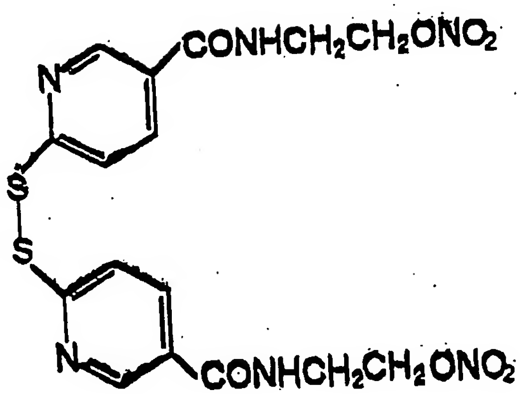
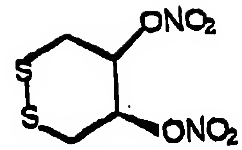

32

6. A pharmaceutical composition for the treatment of disorders where a nitric oxide donors are indicated, which comprises as active ingredient an organic compound containing at least one nitric oxide donor group, and at least one group being, or being converted *in vivo* to a free sulfhydryl group.

7. A composition according to claim 6, where the active compound is one which contains at least one sulfhydryl group, either in the reduced -SH form or in the oxidized -S-S disulfide form.

8. A composition according to claim 6 or 7, where the active compound contains a 5- or 6-membered ring compound containing 2 conjugate -S- atoms, substituted by one or more $-ONO_2$ groups or linked to one or more substituents bearing a terminal $-ONO_2$ group, or where the -S-S group is in an open configuration, linked to at least one aromatic nucleus or a heterocyclic nucleus with a nitrogen in the ring structure, which rings bear a substituent with a terminal $-ONO_2$ group or where the compound is a five-membered hetrocycle containing a -S- atom and a nitrogen substituted with at least one substituent with a terminal $-ONO_2$ group.

9. A pharmaceutical composition according to claim 6 where the active ingredient is selected from:



1

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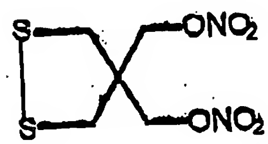

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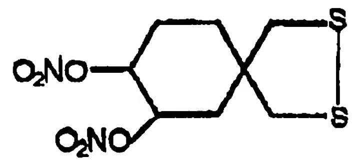

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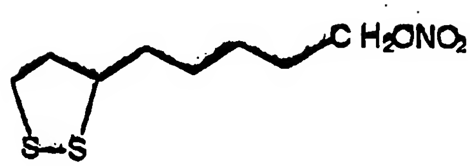

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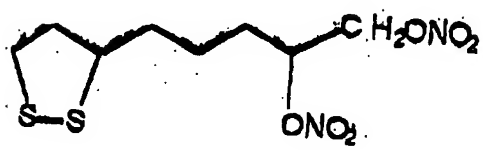

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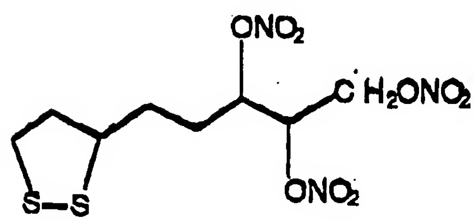

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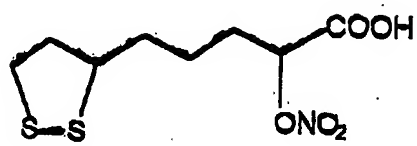

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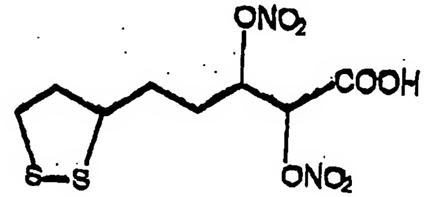

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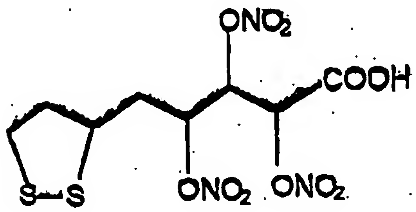

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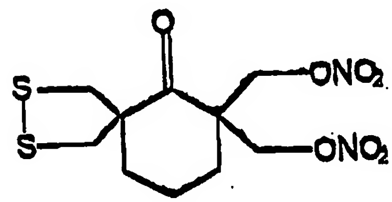

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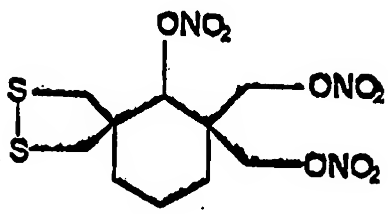

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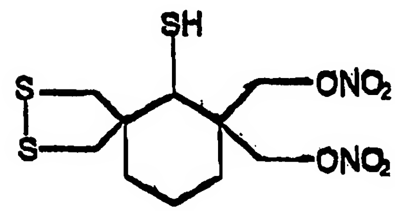

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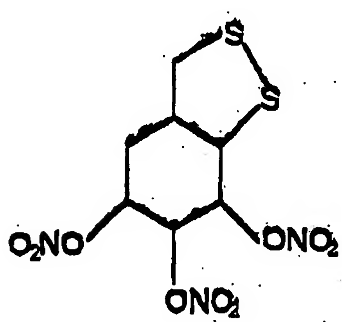

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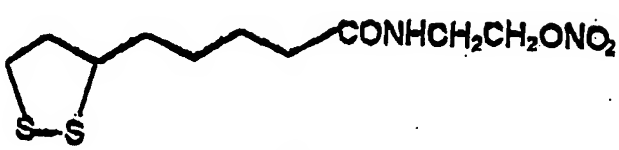

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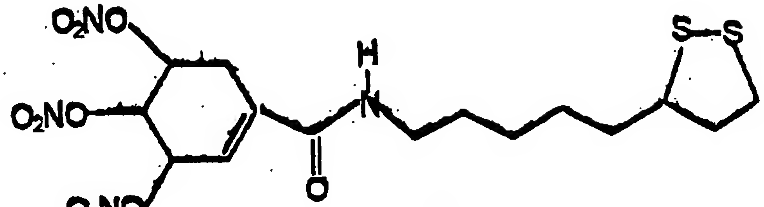

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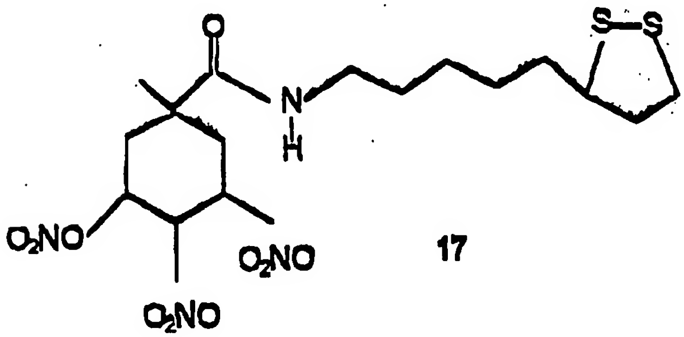

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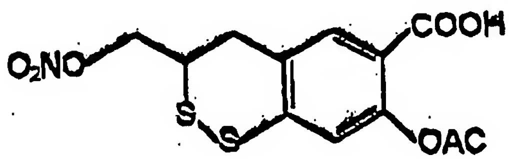

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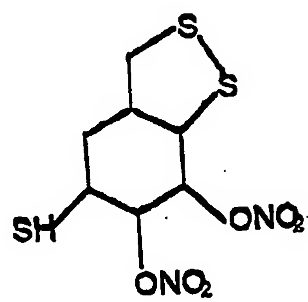

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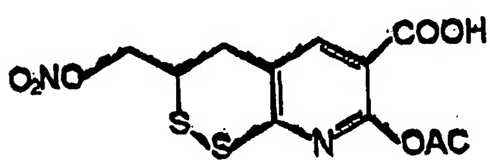

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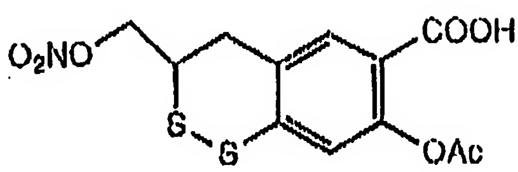

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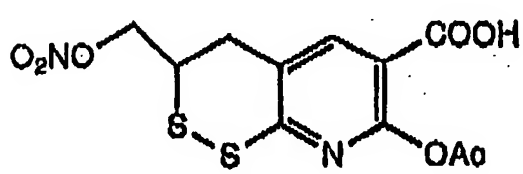

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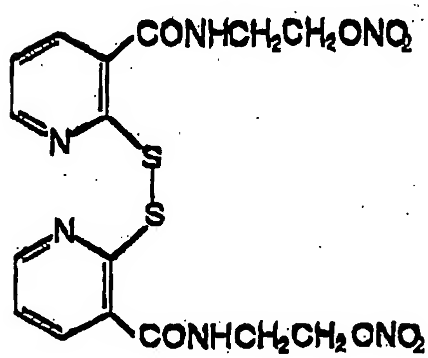

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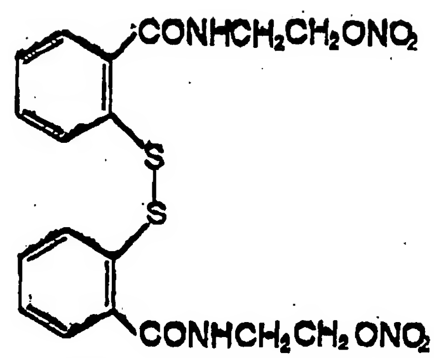

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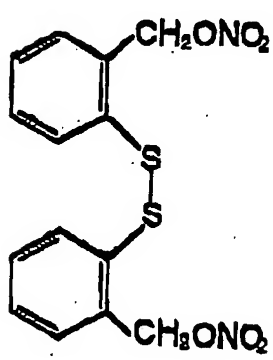

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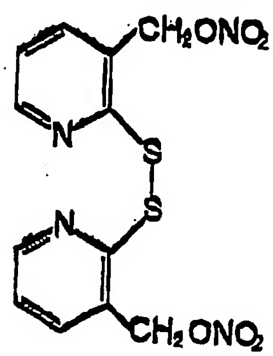

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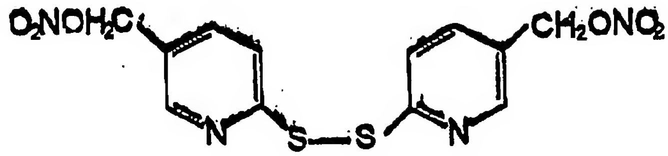
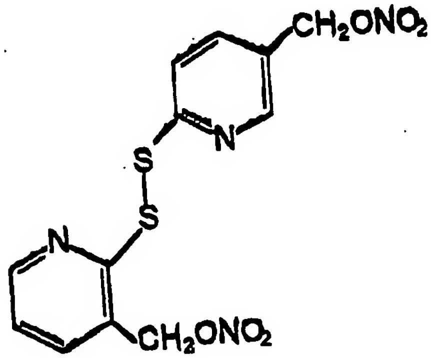
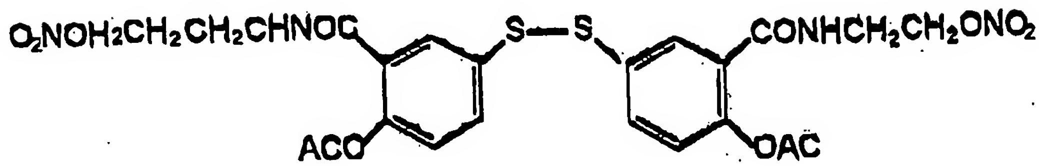

O2NOH2C
CH2ONO2
N
S
S
N

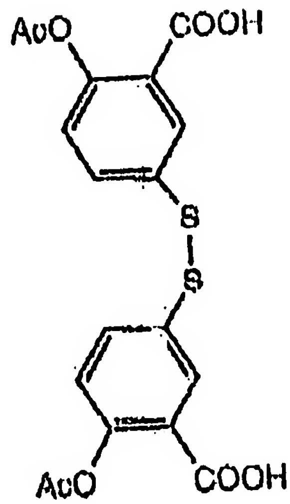
27


CH2ONO2
N
S
S
N
CH2ONO2

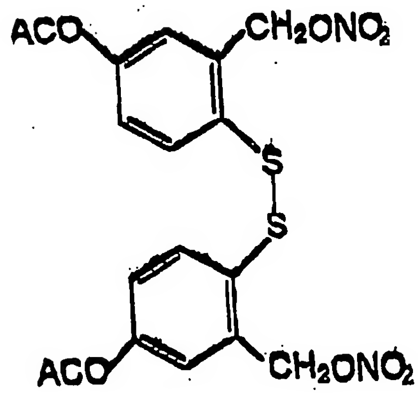
28


O2NOH2CH2CH2CHNOC
S
S
CONHCH2CH2ONO2
ACO
OAC

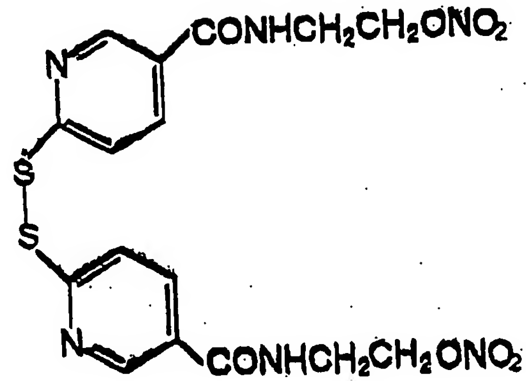
29


AcO
COOH
S
S
AcO
COOH

30

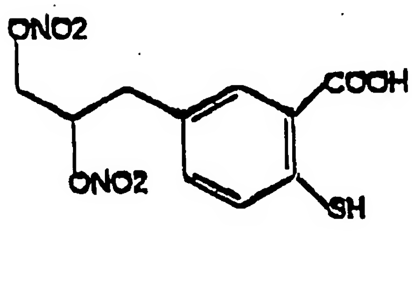

ACO
$CH_2ONO_2$
S
S
ACO
$CH_2ONO_2$

31


N
$CONHCH_2CH_2ONO_2$
S
S
N
$CONHCH_2CH_2ONO_2$

32

10. A pharmaceutical composition according to Claim 6, where the active compound is selected from:

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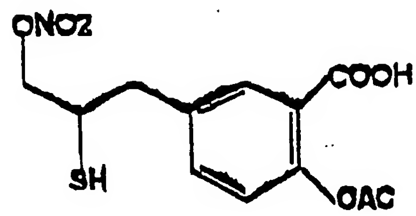


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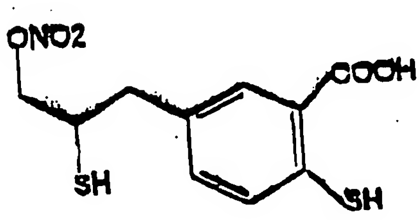


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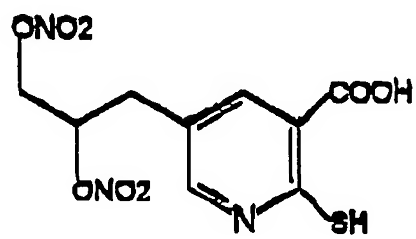


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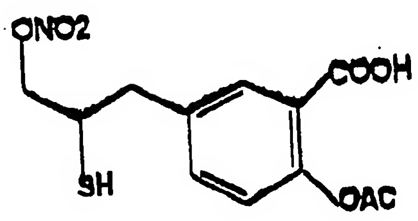


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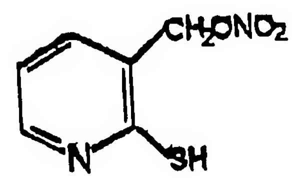


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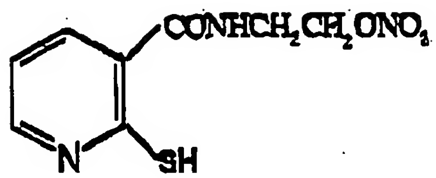

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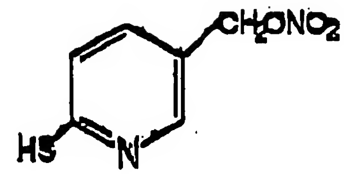

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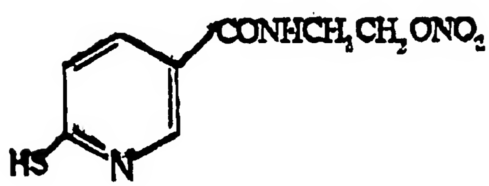

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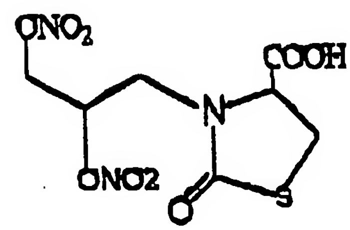

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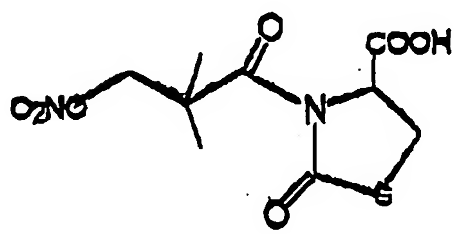

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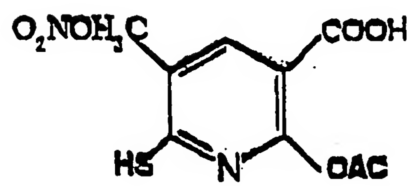

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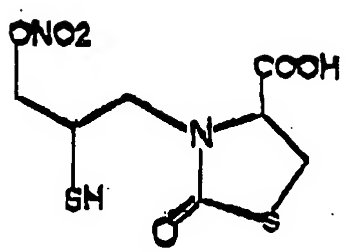
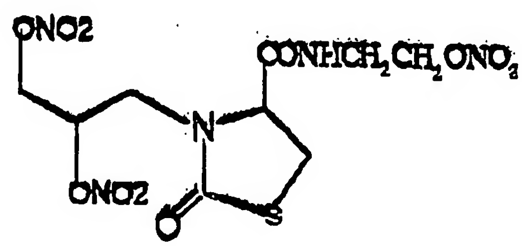
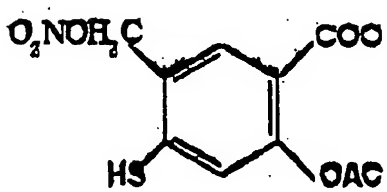

ONO2
COOH
N
SH
O
S

13


ONO2
CONHCH2CH2ONO2
N
ONO2
O
S

14


O2NOH2C
COO
HS
OAC

15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL98/00144

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/114, 261, 296, 297, 298; 548/188; 549/15, 21, 32, 35, 49; 562/ 430; 564/162; 568/22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE Structure Searching In File Registry,File CAPlus,File Beilstein and File Marpat.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | CHEMICAL ABSTRACTS, Vol.125, No.6, 14 October 1996 (Columbus, OH, USA), page 649, column 1, the abstract No. 125:204,523g, SHIRAISHI et al. "Drugs For Improvement of Lipid Metabolism," Jpn. Kokai Tokkyo Koho JP 08,175,994[96,175,994] | 1-10 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

01 AUGUST 1998

Date of mailing of the international search report

01 SEP 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ALAN L. ROTMAN

Della Collins for

Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

## INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL98/00144

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-3 and 6-8
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 1-3 and 6-8 were found unsearchable to the extent that no structure was provided, only substituent groupings or portions of structures.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL98/00144

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07C 321/28, 323/42; C07D 213/62, 213/70, 213/78, 277/06, 327/06,339/02, 339/08, 401/12, 471/04, 487/04

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

546/114, 261, 296, 297, 298; 548/188; 549/15, 21, 32, 35, 49; 562/ 430; 564/162; 568/22

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

GROUP1:Claims (1-3, 6-8)in so far as they read on the inventions of claims 4, 5, 9 and 10 in-part drawn to structures 1-3,5 and 15 wherein the term [X] in the depicted formulas represents O-NO2 or SH and the term [Y] represents SH or O-Ac.The mercapto-benzoic acid derivatives assigned to this Group are classified in Class 562;Subclass 430.

GROUP 11:Claims (1-3, 6-8)in so far as they read on the inventions of claims 4, 5, 9 and 10 in-part drawn to structure four. The involved structure is drawn to a 2-mercapto-3-pyridine-carboxylic acid derivative.

GROUP 111:Claims (1-3, 6-8)in so far as they read on the inventions of claims 4, 5, 9 and 10 in-part drawn to structures 6-9 and 12. The depicted Group 111 structures represent 2-mercaptopyridine 3-carboxamido-N-lower-alylene nitrate and 2-mercapto-pyridine lower-alkylene nitrate and derivatives.

GROUP IV:Claims (1-3, 6-8)in so far as they read on the inventions of claims 4, 5, 9 and 10 in-part drawn to structures 10,11,13 and 14. The depicted Group IV structures represent 2-oxazolidine-4-carboxylic acid derivatives.

GROUP V:Claims (1-3, 6-8)in so far as they read on the inventions of claims 5 and 10 in-part drawn to structure 1, which represents 1,2-dithiane-4,5-dinitrate compound.

GROUP V1:Claims (1-3, 6-8)in so far as they read on the inventions of claims 5 and 10 in-part drawn to structure 1,which represents an acyclic disulfide-dinitrate.

GROUP V11:Claims (1-3, 6-8)in so far as they read on the inventions of claims 5 and 10 in-part drawn to structures 3,5-10 and 15-17, which represents 1,2-dithiolane di-or trinitrate derivatives.

GROUP V111:Claims (1-3, 6-8)in so far as they read on the inventions of claims 5 and 10 in-part drawn to structures 4,12 and 13,which represent spiro-1,2-dithiolane derivatives.

GROUP 1X:Claims (1-3, 6-8)in so far as they read on the inventions of claims 5 and 10 in-part drawn to structures 14 and 19,which represent hexahydro-benzo-1,2-dithioles.

GROUP X:Claims (1-3, 6-8)in so far as they read on the inventions of claims 5 and 10 in-part drawn to structures 18 and 21,which represent benzo-1,2-dithiin derivatives.

GROUP X1:Claims (1-3, 6-8)in so far as they read on the inventions of claims 5 and 10 in-part drawn to structures 20 and 22,which represent pyrido-1,2-dithiin derivatives.

GROUP X11:Claims (1-3, 6-8)in so far as they read on the inventions of claims 5 and 10 in-part drawn to structures 23, and 26-28,which represent bis-(4-pyridyl-sulfide) derivatives.

GROUP X111:Claims (1-3, 6-8)in so far as they read on the inventions of claims 5 and 10 in-part drawn to structures 24,25 and 29,which represent bis-(2-phenylcarboxamido-N-ethylene-nitrate derivatives.

The inventions listed as Groups 1-X111 do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: There is no single common core or nucleus and each core does not possess the same pharmacological properties.